MECHANISM OF THE EMETIC ACTION OF NICOTINE AND LOBELINE

by

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A thesis submitted to the faculty of the University of Utah in partial fulfillment of the requirements for the degree of

MASTER OF SCIENCE

Department of Pharmacology

College of Medicine

University of Utah

February, 1957

This Thesis for the M.S. degree

by

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ACKNOWLEDGEMENT

The author wishes to thank Dr. Herbert L. Borison for his patient guidance, constructive criticism and instructive discussions concerning research fundamentals during the course of the present investigation. The author also wishes to thank Dr. Louis S. Goodman and the members of the Departments of Pharmacology, College of Medicine and College of Pharmacy, for their guidance during the author's graduate program.

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INTRODUCTION

A. Historical Background on Nicotine- and Lobeline- induced Emesis.

Nicotine and lobeline long have been known to be emetic agents. Smoking of tobacco, particularly by the uninitiated, is associated with nausea, gastrointestinal distress and frequently vomiting. That lobeline has actions similar to nicotine was demonstrated by the Rev. Manasse Gutler who in 1775 introduced the crude drug into medicine as an emetic (Whitehead and Elliott, 1927). Samuel Thomson so extensively employed the crude extracts of Lobelia inflata in his system of medicine that he commonly was called an "Emetic Doctor" (Ball, 1925). Nicotine was first isolated by Posselt and Reimann (see Jackson, 1941) and lobeline by Weiland and Mayer (see Norris and Weiss, 1927). According to Weiland and Mayer, alpha-lobeline does not possess any emetic action or stimulate autonomic nerve endings, but is a specific respiratory stimulant. The efficacy of this agent as an emetic, however, has been adequately demonstrated by Camp (1927) and by Norris and Weiss (1927).

Nicotine was shown to produce vomiting in eviscerated animals (Eggleston and Hatcher, 1915) and after topical application to the floor of the fourth ventricle (Hatcher and Weiss, 1923). Both groups concluded that nicotine acts by direct stimulation of the medullary vomiting center. To the writer's knowledge, no further experimentation has been conducted to establish more definitely the locus of the emetic action of this drug.

In the past few years, Borison and Wang have presented evidence (which will be reviewed in the next sections of this thesis) to establish the fact that no emetic agent acts by direct stimulation of the vomiting center. All emetic stimuli have been demonstrated to act at other loci and to activate the emetic center through afferent nervous pathways. Therefore, it was felt profitable to reinvestigate the emetic action of nicotine in the light of the more modern concepts of the emetic mechanism and to establish more definitively its locus of emetic action.

Eggleston (1916) found that intravenous atropine, in doses of 0.0035 - 0.05 mg./kg., reduced the incidence of emesis in response to subsequently administered nicotine. He believed that nicotine acted directly on the vomiting center and that atropine desensitized that portion of the vomiting center then believed to be responsive to nicotine. However, Hatcher and Weiss (1928) were unable to prevent the vomiting response to parenterally administered nicotine by prior application of atropine to the dorsal medullary surface and they concluded that the heart is the site of the emetic action of nicotine, for atropine was then believed to block visceral afferent impulses from that organ. Cheymol and Quinquaud, on the other hand, did find that topical application of atropine (1950) to the medulla oblongata, as well as of ergotamine (1948), blocked nicotine-induced emesis. In addition, Hatcher and French (1932) also found that ergotamine, administered intramuscularly, reduced the incidence of nicotine-induced vomiting. Thus the evidence available indicates that nicotine acts at some as yet undefined locus elsewhere than in the gastrointestinal tract to produce vomiting.

Anti-emetic properties also have been claimed for nicotine. Eddy and Hatcher (1928) found that nicotine, given repeatedly at half-hour intervals, made cats refractory to the emetic effects of squill. Other animals which were treated similarly with nicotine, vomited in response to apomorphine; thus, the procedure was not believed to impair the functional integrity of the vomiting center. A similar protective effect of nicotine was observed by Hatcher and Weiss (1928) against oubain, strophanthin, and cymarin. Regardless of the degree of protection afforded by nicotine, the fact that all of the animals tested with digitalis died soon after the drug administration complicates interpretation of these results.

Edmunds in 1904 demonstrated that small doses of an amorphous extract of Lobelia caused repeated vomiting in cats but that larger doses caused only

panting and convulsions without emesis. This author states that the locus of the emetic action is on the vomiting center because larger doses are required orally than parenterally to produce similar emetic effects. Norris and Weiss (1927) also were able to produce vomiting in cats with alpha-lobeline, thus disputing the result of Weiland and Mayer (see above). Norris and Weiss also found that atropine blocked the emetic effects of alpha-lobeline; these results paralleled those of Eggleston (1916) for nicotine. Alpha-lobeline-induced vomiting also has been produced in dogs, even after sedation with chloral hydrate (Camp, 1927).

Hatcher and Weiss (1923) found that removal of either the corpora quadrigemina or the cerebellum failed to prevent the vomiting to lobeline. Decerebration of the cat has been shown not to prevent the emetic response to lobeline sulfate (Borison and Wang, 1949). Borison and Fairbanks (1952) have shown that bilateral nodose ganglionectomy failed to make cats refractory to this agent.

Clementi (1936) found that lobelanine and lobelanidine, secondary alkaloids of Lobelia inflata, both caused vomiting when administered either subcutaneously or topically to the dorsal medullary surface. In addition, lobelanine caused respiratory stimulation and convulsions, whereas lobelanidine was devoid of such effects but had stronger curariform and emetic properties. Lendle and Richter (1950) and Richter (1939) disputed the results of Clementi, stating that lobelanine, lobelanidine and even lobeline were inactivated in the gastrointestinal tract or in the liver and that the emetic potency of Lobelia tincture was dependent upon the isolobinine content, which they found to induce vomiting reflexly by stimulation of the gastric mucous membrane.

Nicotine and lobeline are practically devoid of therapeutic importance but are of considerable pharmacological and toxicological interest. Their actions are similar in that both first stimulate and, with higher doses, depress autonomic ganglia, adrenal medulla, and central nervous system. They have a curariform

action on skeletal muscle, and directly stimulate the vascular and intestinal musculature. Furthermore the peripheral respiratory chemoreceptors and the medullary respiratory and vasomotor centers are stimulated and the hypothalamic-hypophyseal structures are activated with consequent release of ADH. Whereas the respiration can be blocked at the medullary level by both of these drugs, the doses required are higher than those which bring forth the curariform properties of the drugs and death is due to skeletal muscular paralysis (Goodman and Gilman, 1955).

The ubiquitous pharmacological actions of these alkaloids in the body necessitate the formulation of a comprehensive plan of investigation in order to determine the locus of a specific action. An attempt at such an investigation is presented in this thesis. For the sake of orientation in this complex field of investigation, it seems desirable to review briefly the current concepts of the central emetic mechanisms and the present knowledge of the receptor sites and afferent pathways involved in emesis.

B. Current Concepts of the Central Emetic Mechanisms.

Vomiting is a complex, coordinated process which involves both somatic and visceral muscular activity. Prodromata of vomiting include salivation, licking and swallowing, changes in respiration, assumption of characteristic posture and finally retching. The emetic act usually is preceded by a series of coordinated pumping movements of the thoracic and abdominal respiratory musculature, following closure of the glottis, forward extension of the neck, opening of the mouth and protrusion of the tongue. The actual expulsion of the vomitus occurs at the peak of a sustained inspiration.

A large number of functional units are thus brought into play in a systematic manner in order to accomplish the vomiting act. It can readily be seen why Giannuzzi, in 1865, postulated the existence of a "center" to control this panorama of events (see Borison and Wang, 1953). Thumas claimed to have

localized this "center" when, in 1891, he ablated structures in the midline region of the calamus scriptorius and found his animals refractory to the emetic effects of apomorphine, tartar emetic and central faradic vagal stimulation. Hatcher and Weiss (1923) disputed the results of Thumas because they found that, while the lesion which Thumas described resulted in refractoriness to parenteral apomorphine, it did not prevent the vomiting to oral mercuric chloride. These workers believed the vomiting center to be located superficially in the region of the ala cinerea, for lesions here resulted in refractoriness to both emetic agents. However, this conclusion was based only on acute experiments and subsequent investigations in this field have demonstrated that results from acute and chronic experimentation are frequently at variance. The more recent historical development of investigations on the mechanism of vomiting have been reviewed by Borison and Wang (1953), and the older literature by Hatcher and Weiss (1924).

The first strong evidence for the location of the vomiting center was presented by Borison and Wang (1949) who reported that electrical stimulation, in the cat, of an area in the dorso-lateral reticular formation and impinging upon the tractus solitarius produced emetic responses. These positive results placed the center deep to the surface of the medulla; stimulation of the more superficial structures, which had been implicated by earlier workers, failed to cause vomiting. This finding has been confirmed recently by Kuru and Sugihara (1955) although these workers stress the involvement of the fasciculus solitarius to a greater extent than do Borison and Wang.

To investigate further the role of the superficial medullary structures, Wang and Borison (1950) prepared chronic animals in which superficial as well as deep structures were destroyed by electrocautery. Moreover, they were able, with the use of radon implants, to destroy selectively the dorso-lateral reticular tissues without damaging surface structures (Wang and Borison, 1951). Both the

surface and the deep structures were found to be important in emesis, the former to be the receptor site for the emetic action of apomorphine (emetic chemoreceptor trigger (CT)-zone), whereas the latter was recognized to be the vomiting center per se. The superficial area in the region of the ala cinerea was inactive, however, in the absence of the emetic center.

Additional support for the localization of the emetic center in the medulla is seen in the experiments of Thumas (1891) who produced vomiting with apomorphine in a dog after brain stem section at the level of the acoustic striae. Hatcher and Weiss (1923) induced emesis with lobeline after cerebellectomy, as previously mentioned. Borison and Fairbanks (1952) reported that cats vomited to Veriloid following low cervical cord section. It is evident therefore that, provided the neural motor pathways essential for the accomplishment of the vomiting act are intact, the medulla oblongata alone is capable of coordinating the functional systems necessary to produce vomiting. It is this coordination of functions which is the essence of the modern concept of the emetic center. The center, as described by Borison and Wang (1949) and Kuru and Sugihara (1955), is located dorsal to the inspiratory component of the respiratory integrator mechanism, and ventral to the respiratory pacemaker area (Brodie and Borison, 1957) and to the area controlling spasmodic respiratory acts (Borison, 1948). In addition, it lies immediately ventral to the salivatory nuclei (Wang, 1943), and in the midst of the reticular formation demonstrated by Magoun (1950) to modify somatic motor activity. This aggregation of functional units acts in a cohesive fashion to organize the entire body for the accomplishment of emesis. The vomiting center is therefore not an isolated center, but rather an integrator mechanism at which the aforementioned centers produce vomiting by combined forces.

The CT-zone has been seen to be a receptor site, functioning through the emetic center. Thus, certain centrally-acting emetic agents have been shown

to act external to the vomiting center. Indeed, in subsequent experimentation based on this new working hypothesis, no agent has been found to produce emesis by a direct action on the medullary reticular center. This conclusion is supported by the fact that it can always be demonstrated that animals insensitive to one class of emetic agents, as a result of interruption of certain afferent pathways, can be made to vomit following the administration of a member from another class of drugs. In this way it can be demonstrated irrefutably that selective refractoriness to an emetic agent is due to interruption of a particular pathway or pathways and not due to non-specific central neuronal depression or motor incapacitation of the emetic reflex mechanism.

C. Receptor Sites and Afferent Pathways in Emesis.

A list of the postulated receptor sites for the emetic action of various agents is presented in table 1. It will be seen that electrical stimulation of three areas rostral to the rhombencephalon has been shown to cause vomiting (Penfield and Rasmussen, 1950; Hess, 1954; Penfield and Welch, 1951). The emesis from these rostral structures occurred only after prolonged stimulation or after stimulation had ceased. Therefore it seems probable that these are not primary emetic centers, if they are centers at all, and that they probably can be considered as receptor sites sending afferents to the bulbar center. However, these tissues have never been stimulated following excision of the medullary center and can not be excluded as independent secondary centers. Stimulation of the paracentral sulcus in the human (Penfield and Welch, 1951) has been found to cause a "desire to vomit" and may therefore be more closely affiliated with the psyche than with efferent activity.

Many agents are listed as acting by stimulation of the CT-zone of the medulla oblongata. The evidence in favor of apomorphine, morphine and Hydergine acting at this site seems well substantiated. However, an action of X-radiation here is

ıble 1. Proposed Sites of Action of Emetic Agents in the Body.

)breviations used for routes of administration: I.V. = intravenous; P.O. = per os; 3 V. = per third ventricle; L.V. = per lateral ventricle; I.T. = intrathecally; I.P. = intraperitoneally.

I. Cerebral

Agent	Route	Species	Locus of Action	Pathway	Reference
lectrical timulation		Human	Island of Reil	Direct to medullary center or through a hypothalamic relay	Penfield & Rasmu 1950
lectrical timulation		Human	Paracentral sulcus*	as above	Penfield & Welch 1951
itrogen ustard	I.V.	Cat	Cerebral cortex (?)	as above	Brand et al., 19
ilocarpine	I.V.	Cat	Frontal lobe	as above	Borison et al.,
ilocarpine pituitrin	L.V.	Human	Hypothalamus	as above	Cushing, 1931
cetylcholine eserine	L.V.	Human	-		Henderson & Wils 1936
eostigmine	I.T.	Human	-		Kremer, 1942
serine	L.V.	Cat	-		Feldberg & Sherw 1954
taphylococcus nterotoxin	I.P.	Cat	Hypothalamus	as above	Borison et al., (Bayliss, 1940)†
lectrical timulation		Cat	Hypothalamus lateralis	as above	Hess, 1954

† "Desire to vomit" produced

- Emphasized role of the vagus

- Not specified by authors

able 1. (cont.)

II. Lower Brain Stem

Agent	Route	Species	Locus of Action	Pathway	Reference
lectrical timulation		Cat	Lateral reticular formation		Borison & Wang, 1949
pomorphine	I.V.	Dog	CT-zone	Transmedullary	Wang & Borison, 1950; 1951; 1952
orphine	I.V.	Dog	CT-zone	Transmedullary	Wang & Glaviano, 1
ydergine	I.V.	Dog	CT-zone	Transmedullary	Wang & Glaviano, 1
ardiac-lycosides early phase)	I.V.	Dog	CT-zone	Transmedullary	Borison & Wang, 19 Wang & Borison, 19
ardiac-lycosides early phase)	I.V.	Cat	CT-zone	Transmedullary	Borison & Brizzee, 1951
ardiac-lycosides	3 V.	Dog	CT-zone #	Transmedullary	Weinberg & Haley, Haley, 1956
opper ulfate	I.V.	Dog	CT-zone	Transmedullary	Wang & Borison, 19 1952
-radiation		Dog	CT-zone	Transmedullary	Chinn & Wang, 1954
-radiation		Monkey	CT-zone (?)	Interposed transmedullary	Brizzee et al., 19
lotion		Dog	CT-zone (?)	Vestibulo-cerebellar	Wang & Chinn, 1954
lotion		Dog	Labyrinth	Vestibulo-cerebellar	Tyler & Bard, 1949 Wang & Tyson, 1954 Wang & Chinn, 1956 Chinn & Smith, 195

Proposed site, not supported by direct evidence.

Table 1. (cont.)

III. Peripheral

Agent	Route	Species	Locus of Action	Pathway	Reference
Electrical stimulation		Cat		Vagus	Miller, 1910
Electrical stimulation		Cat, dog		Vagus	Derbyshire & Ferg 1938
Electrical stimulation		Cat		Nodose ganglion	See Borison & War 1953
Mustard	P.O.	Cat	Stomach	Vagus	Miller, 1910
Distention of gut		Dog	Pylorus	Vagus	Goldberg, 1931 Herrin & Meek, 19
Distention of gut		Dog	Gall bladder, biliary passages	Vagus, left splanchnic	Schrager & Ivy, 1
Distention of gut		Cat	Ligation of Mesenteric vein		Franklin & McLach 1937
E. coli (peritonitis)			Visceral peritonium	Vagus, sympathetic	Walton et al., 19
Cardiac glycosides (late phase)	P.O.	Dog	Parenteral		Wang & Borison, 1
Cardiac glycosides (late phase)	P.O.	Cat	Parenteral		Borison, 1952
Cardiac glycosides	I.V.	Pigeon	Liver, abdominal viscera	Vagus	Hanzlik & Wood, 1
Copper sulfate	P.O.	Dog	Gut mucosa	Vagus, splanchnic	Wang & Borison, 1 1952
X-radiation		Cat	Abdomen	Vagus, lower thoracic sensory roots	Borison, 1957
X-radiation		Monkey	Abdomen	Vagus	Brizzee, 1956
Veratrum	I.V.	Cat	Nodose ganglion	Vagus	Borison & Fairban 1952 Tanaka & Kanno, 1

disputable. Chinn and Wang (1954) found that lesions in the CT-zone made dogs uniformly refractory to the emetic effects of X-radiation despite the fact that irradiation only of the head never was effective in evoking emesis. Brizzee (1955) reported that ablation of the area postrema of the monkey blocks the vomiting to X-radiation but later found that supradiaphragmatic vagotomy alone made this species insensitive (Brizzee, 1956). Borison (1957) states that cauterization of the CT-zone in cats results in uncertain and unpredictable effects on radiation-induced emesis. This author believes that, for the cat at least, the locus of action is in the abdomen, for supradiaphragmatic vagotomy combined with bilateral dorsal rhizotomy of the lower thoracic segments of the cord desensitizes the animal, as does shielding the abdomen. Therefore, whereas ablation of the CT-zone can cause emetic refractoriness to X-radiation, this area can not be the direct site of action in the cat and the monkey. Neither can the CT-zone be the site of action of a humoral agent released as a result of irradiation since, in the cat, other agents are effective in stimulation of the CT-zone at the same time that radiation is ineffective as an emetic, following interruption of afferent pathways from the abdomen.

Cardiac glycosides and copper sulfate, when administered intravenously, are believed to have their primary emetic action at the CT-zone (Wang and Borison, 1951, 1952; Borison and Wang, 1951; Borison and Brizzee, 1951; Borison, 1952). However, in the cat, Borison (1957) has found no consistent relationship between the emetic responses to apomorphine and to the cardiac glycosides following lesions made in the area postrema. Cats can be refractory to either one or both of these agents and no consistent neurological difference could be detected histologically in lesions of different effectiveness. The evidence indicates that either there are two morphologically and/or physiologically distinct receptor sites in the CT-zone or that one of these agents is acting peripherally. Apomorphine produces emesis

following topical application to the medulla (Hatcher and Weiss, 1923). Its action is prevented by parenteral administration of chlorpromazine, also believed to act at the CT-zone (Brand et al., 1954; Glaviano and Wang, 1955; Cook and Toner, 1954). In addition, cisternal injections of chlorpromazine make animals insensitive to subsequent injections of apomorphine (Glaviano and Wang, 1955). The cardiac glycosides or copper sulfate still cause emesis when administered intravenously following injections of chlorpromazine and the cardiac glycosides are not effective by topical application to the dorsal medullary surface.

The controversial nature of the evidence which has been accumulated in the study of emesis, particularly as regards the locus of emetic action of X-radiation and the cardiac glycosides, makes it imperative that a reinvestigation of the problems be carried out. Such a reappraisal is especially warranted in the light of a recent series of neuro-anatomical investigations. Liu (1956) has demonstrated that, following section of the dorsal roots of the spinal cord of the cat, the intraspinal fibers which degenerate traversed the posterior funiculus and terminated on the dorsal surface of the medulla at the level of the inferior olivary nucleus. Most interesting, perhaps, is the fact that section of the more caudal thoracic roots, namely, those innervating the abdominal viscera, resulted in degeneration of fibers which terminated in the periventricular areas of the medulla oblongata. Kuru (1956) has shown more definitely for the cat, dog, monkey, goat, guinea pig, and human that nerve fibers originating at thoracic, lumbar, and sacral levels course through the anterolateral funiculus of the spinal cord and terminate in the region of the nucleus paraalaris, nucleus juxtasolitarius, and ventral to the descending root of the trigeminal nerve. In the same article, Kuru reports that section of the lateral fascicle in a tabetic patient at the bulbo-spinal junction alleviated gastric crises associated with vomiting. Rostral degeneration took the course of the aforementioned spinobulbar tracts. Kahn (1933) and Kahn and Barney

(1937) similarly relieved gastric crises in eight tabetic patients by anterolateral chordotomy at the level of the eighth cervical segment. Kuru and Sugihara (1955) have attempted to implicate these pathways in emesis. These authors state, "...the chemoreceptor trigger zone mentioned by both authors (Borison and Wang, 1951; Hatcher and Weiss, 1923), situated between the ala cinerea and the vestibular complex and medially contiguous with the area postrema which overlies the ala cinerea, corresponds fairly to the site of termination of the thoraco-bulbar tract". Certainly the proximity of the paraala nucleus of Kuru to the area postrema suggests the possibility that fibers in this area may be interrupted inadvertently in the process of ablating the CT-zone. The limitations imposed by the techniques for making discrete lesions favor such a postulate. Further support to this suggestion is given by the reports of Borison (1957) and Brizzee (1956) who found that, whereas ablation of the CT-zone reduced the sensitivity of the cat and monkey, respectively, to radiation-induced emesis, peripheral lesions were also effective. Therefore, it can be stated that the medullary lesions interrupted afferent pathways and did not destroy receptor sites. Nevertheless, the evidence for a direct action on the CT-zone of certain agents, namely, apomorphine, morphine, and the ergot alkaloids, appears to be more certain than for the cardiac glycosides. This region may be likened to a funnel which channels stimuli to the emetic center, but exactly which agents have their site of action within the "funnel" seems less certain than previously thought. Ablation procedures will have to be refined to produce more circumscribed lesions so as to rule out, as far as possible, the destruction of neighboring pathways. In addition, histochemical techniques may have to be employed to exclude, if possible, the existence of multiple receptors.

Emetic receptors which are located in the neck and trunk and which respond to pharmacological, mechanical, or electrical stimuli are listed in table 1. Possible stimulation of any of these loci as well as all the suprasegmental sites mentioned must be considered when analyzing the mechanism of action of a new emetic

agent. In addition, one must seek new sense organs capable of initiating afferent emetic impulses and consider as well the possibility of multiple sites of action.

D. Anti-Emetic Drugs.

The ideal anti-emetic drug is one which, in non-toxic doses, selectively prevents vomiting from any cause. The logical site of action for such an agent would be the medullary vomiting center, for this is the single locus of integration for all emetic stimuli. However, the vomiting center located in the medullary reticular formation, as previously mentioned, is so intimately concerned with the vital function of respiration that depression of this center can only lead to concomitant respiratory depression. One must therefore look to the specialized receptor sites for the individual emetic stimuli to find the loci at which such an antagonism could take place. The selectivity of emetic receptors for drugs of widely different pharmacological classes also militates against the possibility of discovering a universally-effective anti-emetic drug which could act simultaneously at all receptor sites. We are, therefore, forced to direct our efforts towards finding agents which act either at specific emetic receptor sites, and thereby antagonize only the emetic action of drugs, or which pharmacologically oppose all of the actions of an emetic agent. Earlier research has identified drugs of both groups: chlorpromazine - an agent which acts selectively at the CT-zone and blocks the emetic action of apomorphine, morphine, and Hydergine (Brand et al., 1954), and atropine - an antagonist which blocks all of the muscarinic actions of pilocarpine including the vomiting response to this drug (Kwit and Hatcher, 1933). Drugs of the former class are more desirable for they permit expression of other, possibly beneficial, actions of the emetic substance.

Four drugs were chosen as candidate anti-emetic agents in the present study: chlorpromazine, atropine, tetraethylammonium (TEA), and hexamethonium (C6). The efficacy of chlorpromazine against clinical drug-induced emesis and vomiting secondary to a variety of clinical disorders has been reviewed recently by Connor

and Moyer (1956) and need not be considered here. Reports of investigations concerning the ability of chlorpromazine to inhibit vomiting in experimental animals have been more limited; but they have indicated that the site of anti-emetic action of this drug is the CT-zone. Brand et al., (1954) showed that chlorpromazine (1.5 mg./kg. S.C.), in the dog, raised the threshold for apomorphine-induced emesis from two and one-half to four times and prevented vomiting to uniformly effective emetic doses of morphine and Hydergine, whereas it was ineffective in protecting against intravenous veratrum, lanatoside-C, and copper sulfate. In cats, on the other hand, chlorpromazine failed to inhibit vomiting to drugs which act at the CT-zone, although it reduced the incidence of vomiting to intravenous pilocarpine. Glaviano and Wang (1955) demonstrated that chlorpromazine (2.0 mg./kg. S.C.) raised the threshold for apomorphine- and Hydergine-induced emesis in dogs but they were able to show only moderate protection against morphine with intravenous doses of chlorpromazine up to 6 mg./kg. In contrast, this dose of chlorpromazine afforded complete protection against the emetic action of oral copper sulfate, indicating to the authors that there was depression of the medullary reticular vomiting center. While this appears to be the most probable explanation, it fails to explain the inability of the drug to prevent vomiting to morphine. Boyd et al., (1954) and Cook and Toner (1954) also found that chlorpromazine reduced the incidence of apomorphine-induced emesis in dogs. The same type of antagonism has been demonstrated in man by Isaacs and MacArthur (1954), who showed that chlorpromazine reduced the incidence of vomiting to subcutaneously administered apomorphine from 45 percent to 4 percent.

Chinn and Sheldon (1954) found that chlorpromazine afforded significant protection against radiation-induced vomiting in the dog, whereas Borison et al., (1955 showed that, in the cat, this agent had only a weak inhibitory action against vomiting due to radiation. Cook and Toner (1954) and Chinn and Smith (1955) have reporte that chlorpromazine is effective against swing sickness in dogs but not in humans.

Gujral et al., (1956) and Madjerek and Stern (1956) were unable to inhibit vomiting to digitalis in the pigeon with doses of chlorpromazine up to 10 mg./kg. administered intramuscularly. However, Gujral et al., showed that chlorpromazine did reduce the incidence of emetine-induced vomiting in this species.

The use of atropine as an anti-motion sickness agent has been reviewed by Tyler and Bard (1949) and more recently by Chinn and Smith (1955). The use of atropine as an antagonist of drug-induced vomiting is reviewed briefly below. Eggleston (1916) showed, in dogs, that atropine blocks the vomiting which follows pilocarpine and nicotine but not that which follows morphine, apomorphine, emetine, aconitine, or oubain. Indeed, as little as 0.0035 mg./kg. atropine base, intramuscularly, was reported to block vomiting to 0.35 mg./kg. nicotine base given by the same route. Norris and Weiss (1927) similarly reported that atropine reduced the incidence of vomiting to lobeline. Unfortunately, Norris and Weiss did not present data to support their statement. Koppanyi (1930) found in dogs that introduction of copper sulfate and cephaeline into a duodenal pouch produced emesis, and that a high concentration of atropine by the same route blocked the vomiting. Intravenous atropine, however, was ineffective. It seems likely that atropine, under these conditions, act as a local anesthetic. Hatcher and Weiss (1928) showed that atropine reduced the frequency but not the incidence of strophanthin-induced vomiting in cats. Kwit and Hatcher (1933) demonstrated that atropine prevented both the emesis and the pre-emetic prodromata following pilocarpine administration in the cat. On the basis of this antagonism, the authors postulated that pilocarpine had a peripheral site of emetic action, most probably at the heart. Borison et al., (1956) have shown, however, that pilocarpine acts on frontal lobe structures to produce emesis. Atropin injected either intramuscularly or into the lateral cerebral ventricles, prevents vomiting to a subsequent intraventricular injection of either pilocarpine or pituitri (Cushing, 1931).

Swiss (1952) used tetraethylammonium (TEA), as well as scopolamine, atropine, ephedrine, Dibenamine, and methanthaline in an attempt to find a pharmacological antagonist of veratrum-induced emesis in dogs. None of these agents blocked the vomiting to veratrum. Busse and Lendle (1953) screened TEA, pendiomide, and scopolamine-N-bromobutylate, as well as nicotine, procaine, papaverine and Dibenamine for anti-emetic potency against nicotine, apomorphine, pilocarpine and the digitalis glycosides. TEA (10-20 mg./kg.), pendiomide (0.2 mg./kg.), and scopolamine-N-bromobutylate (10-20 mg./kg.) were effective in preventing nicotine-induced vomiting. In addition, the scopolamine salt was effective in preventing vomiting to pilocarpine. None of the other drugs listed was found to have anti-emetic potency against apomorphine, nicotine, pilocarpine, or the digitalis glycosides.

To the author's knowledge, hexamethonium (C6) has never been assayed for anti-emetic potency. However, in view of the fact that Busse and Lendle (loc. cit.) demonstrated that drugs with ganglionic blocking properties could inhibit nicotine-induced emesis in dogs, it was thought profitable to test C6 against nicotine and lobeline-induced emesis, as well as to extend these studies to include cats.

METHODS

A. General Procedures.

Twenty-one acute and forty-five chronic experiments were performed on cats and ten chronic experiments were performed on dogs, for localization of site of emetic action of nicotine and lobeline. All acute surgery was performed under ether anesthesia and the cats were tested at least one hour after discontinuation of the anesthetic. Chronic animals routinely were given 300,000 units of procaine penicillin in aqueous solution intramuscularly immediately after surgery. Animals which did not eat voluntarily in the post-operative state were either force-fed orally or maintained with parenteral glucose and saline solutions. Whenever possible animals were fed immediately before testing with the emetic agents. In cases in which the abdominal musculature was paralyzed, owing to spinal transection, a binder was put on the abdomen so as to facilitate the mechanical process of vomiting.

For routine drug tests, animals were selected at random from a stock supply and they were fed shortly before injection. Caution was exercised to avoid reuse of animals at short intervals. The animals were restrained only during injection of the drugs. Cats were returned to their cages and dogs were collared and restricted to a small area. All animals were observed constantly for at least 30 minutes after injection of either nicotine bitartrate or lobeline sulfate, unless vomiting occurred earlier. Nicotine bitartrate and lobeline sulfate in physiological saline solution were prepared fresh on the day of the test. These alkaloids were injected intramuscularly. Atropine sulfate, TEA bromide, and C6 chloride also were dissolved in physiological saline solution on the day of the test. In the drug antagonist studies, TEA and C6 were injected 10 minutes and atropine and chlorpromazine 30 minutes before nicotine bitartrate or lobeline sulfate. TEA, C6, and atropine were injected intramuscularly; chlorpromazine was injected subcutaneously.

B. Surgical Techniques.

1. Decerebration. The common carotid arteries were ligated in the mid-cervical region. The cranium was then opened and the dura mater incised. A flexible spatula was inserted along the rostral surface of the tentorium and the brain stem sectioned at the level of the superior colliculi. The forebrain was then removed and the cavity packed with cotton soaked in physiological saline solution.

2. Vagotomy. The vagus nerves were sectioned under aseptic conditions at one of three levels: a) supradiaphragmatic, b) subclavian, and c) mid-cervical. In the case of the supradiaphragmatic and right subclavian vagotomies, the animals were maintained on positive pressure artificial ventilation while the pleural cavity was open. The procedures were accomplished by the most direct surgical approach. In the case of bilateral mid-cervical vagotomy, it was necessary to establish an airway prior to section of the vagus nerves which include the recurrent laryngeal nerve. This was accomplished by one of the following operations: a) vocal cord removal, b) establishment of a tracheal fistula, or c) insertion of a tracheal cannula.

3. Spinal Cord Transection and Dorsal Rhizotomy. The desired segment(s) of the spinal cord was located by use of the spinous process of the first thoracic vertebra as a point of reference. The soft tissues were separated from the bone and a laminectomy was performed. In the case of spinal cord transection, only the dorsal surface of the dura was incised, thus preventing dislocation of the cord after transection. A similar surgical approach was carried out for sectioning the dorsal roots. After laminectomy, the roots were cut either intradurally or extradurally. When the rhizotomy was performed intradurally, the dura was incised longitudinally and the dorsal roots were lifted and sectioned at the point of entry into the cord. In order to section the roots extradurally, the laminectomy had to be extended laterally and the intervertebral fat pads removed. The dorsal roots were lifted and sectioned central to the ganglion.

4. Medullary Lesions. The animal was maintained on positive-pressure artificial ventilation so as to prevent death from apnea which might result from temporary medullary depression due to the surgical trauma. The head was fixed in a head holder and ventroflexed to permit complete exposure of dorsal structures. The skin and soft tissues were incised with a cold cautery scalpel and retracted widely. The foramen magnum was then extended dorsally and laterally and the dura and arachnoid membranes were cut. The cerebellum was lifted with a spatula and the floor of the fourth ventricle exposed. Superficial lesions were made on the dorsal medullary surface with either a heat cautery or, in a few cases, with a sharp curved scalpel blade. The dura was approximated at two or three points and the incision closed.

RESULTS

A. Emetic Dose of Nicotine Bitartrate and Lobeline Sulfate.

Prior to experimental analysis of the emetic mechanism, it was necessary to establish consistently effective emetic doses of nicotine bitartrate and lobeline sulfate. Cats and dogs were injected intramuscularly with doses of these drugs ranging from 0.25 to 6.0 mg./kg. The lowest dose of nicotine bitartrate which produced emesis in 100 percent of the cats and dogs tested was 1.5 mg./kg. The minimal uniformly effective emetic dose of lobeline sulfate for all cats and dogs tested was 0.5 mg./kg. It will be seen in table 2, for nicotine bitartrate, and in table 3, for lobeline sulfate, that doses up to 6.0 mg./kg. of the drugs also consistently produced vomiting. The apparent difference, as seen in these tables, is in reality very slight for, as seen in figure 1, when calculated as dose of alkaloid base the minimal uniformly effective emetic dose is 0.49 mg./kg. of nicotine and 0.39 mg./kg. of lobeline. This close quantitative relationship of the two drugs for both species coincided throughout the entire dose-effect relationship.

The prodromata of vomiting were similar for both species. Both cats and dogs exhibited salivation, agitation, increases in respiration leading to panting, and frequently defecation and/or micturition. In addition, the pinnae of cats were activated and spontaneous ear flicking was seen for the duration of the hyperpnea. Cats also vocalized immediately prior to the expulsion of the gastric contents. The respiratory change and salivation, as well as agitation, were also seen after doses which were ineffective in evoking emesis.

In a few cases, the dosages used exceeded 6.0 mg./kg. One cat received 12.0 mg./kg. of lobeline sulfate and another 36.0 mg./kg. of this agent. The response to the lower of the two doses differed from that already described only in degree, whereas the higher dose evoked, in addition, a series of clonic convulsions approximately 12 minutes after the injection. This cat vomited after a prolonged latency of 85 minutes.

Table 2

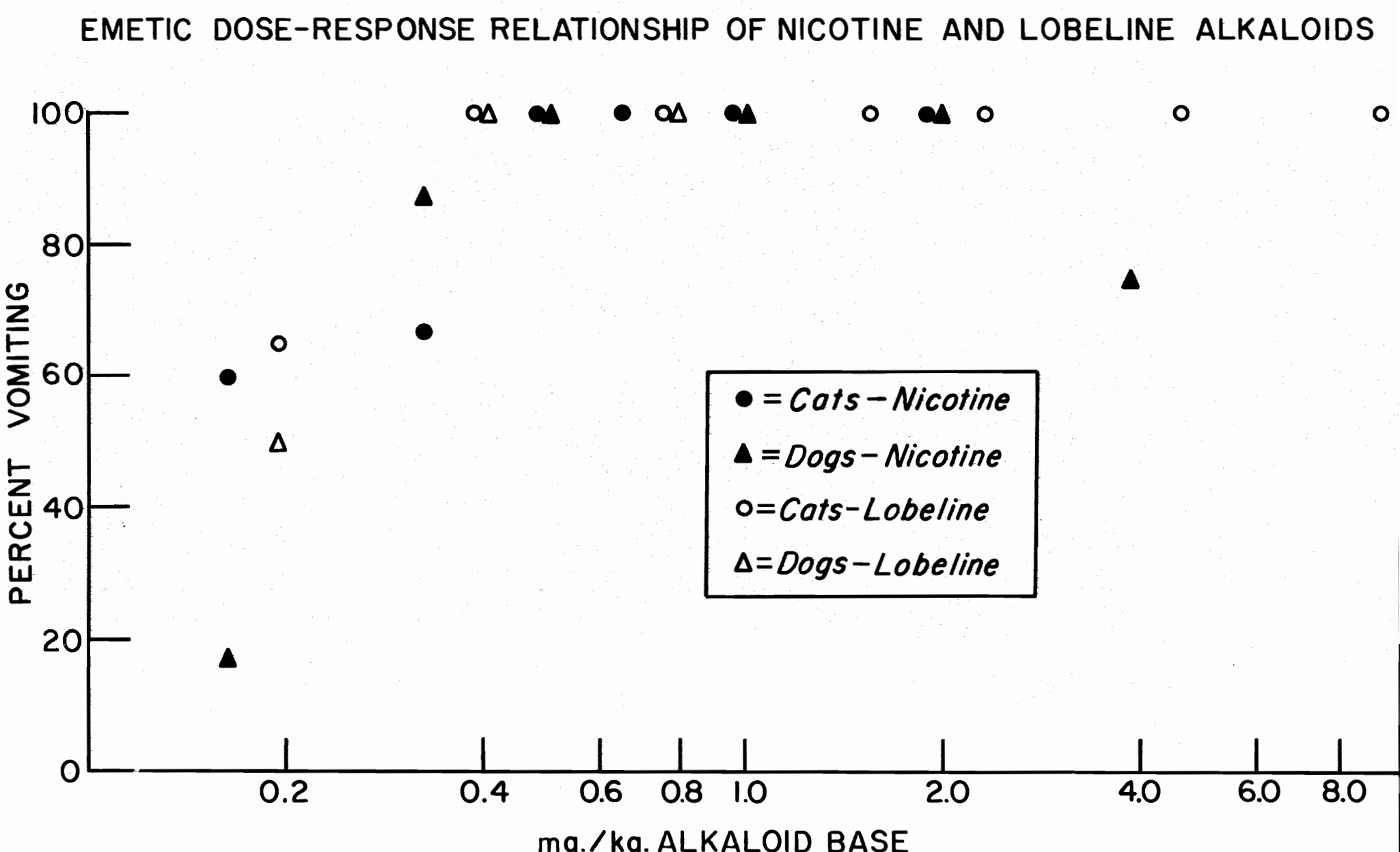
EMETIC DOSE-RESPONSE RELATIONSHIP OF NICOTINE BITARTRATE (I.M.)

DOSE	CATS			DOGS		
mg./kg.	No. tested	No. vomited	Latency (range) min.	No. tested	No. vomited	Latency (range) min.
0.25	8	1	6			
0.5	10	6	5.5(3-9)	6	1	10
1.0	12	8	7.5(4-15)	8	7	10.6(5-15)
1.5	11	11	8.1(4-15)	14	14	9.2(7-14)
2.0	4	4	4.9(4-7)			
3.0	4	4	5.8(4-8)	4	4	7.7(5-12)
6.0	3	3	2.8(2.5-3)	4	4	7.3(5-9)
12.0				10	6	12.6(4-27)

Table 3

EMETIC DOSE-RESPONSE RELATIONSHIP OF LOBELINE SULFATE (I.M.)

DOSE	CATS			DOGS		
mg./kg.	No. tested	No. vomited	Latency (range) min.	No. tested	No. vomited	Latency (range) min.
0.25	3	2	5, 6	2	1	5
0.5	6	6	5.5(2.5-9)	5	5	6.6 (5-9)
1.0	6	6	3.9(3-5.5)	6	6	5.2 (3-9)
2.0	2	2	2.5, 4			
3.0	5	5	3.6(3-5)			
6.0	3	3	3 (2-4)			
12.0	1	1	1			
36.0	1	1	85			


EMETIC DOSE-RESPONSE RELATIONSHIP OF NICOTINE AND LOBELINE ALKALOIDS
PERCENT VOMITING
100
80
60
40
20
0
0.2
0.4
0.6
0.8
1.0
2.0
4.0
6.0
8.0
mg./kg. ALKALOID BASE
● = Cats – Nicotine
▲ = Dogs – Nicotine
○ = Cats – Lobeline
△ = Dogs – Lobeline

Ten dogs were injected intramuscularly with 12.0 mg./kg. nicotine bitartrate. Within the first three minutes after the injection all of the dogs became ataxic. Concomitantly, salivation became so excessive that the dogs appeared to be frothing at the mouth. Six of the ten dogs vomited between four and twenty-seven minutes after the injection; the remaining dogs did not vomit. Vomiting was so severe that the intestinal as well as the gastric contents were expelled. All ten animals exhibited relaxation of the nictitating membrane, muscular fasciculations of the trunk and extremities, and collapse. Three of the four dogs which failed to vomit in response to 12.0 mg./kg. nicotine bitartrate, had a convulsion within the first five minutes after injection.

B. Surgical Results.

1. Chronic Medullary Lesions. Owing to the importance of the CT-zone as a central receptor site for the emetic action of drugs, it seemed desirable to investigate the possible role of this site in nicotine-and lobeline-induced vomiting. Seven dogs with chronic lesions of the CT-zone were tested nine times with the standard emetic dose of nicotine bitartrate (1.5 mg./kg. I.M.) and vomiting was not evoked in any of the tests. Three of the seven dogs were also refractory to 100 µg./kg. I.V. of apomorphine--more than five times the average threshold emetic dose, thus indicating that the CT-zone had been effectively removed; the remaining dogs were refractory to at least 50 µg./kg. I.V. apomorphine.

Two other dogs with chronic ablation of the CT-zone were studied more intensivel The first dog was insensitive to the emetic effects of 3.0 and 6.0 mg./kg. I.M. nicotine bitartrate and to 1.5 but not 3.0 mg./kg. I.M. lobeline sulfate. Surprising this animal vomited following 50 µg./kg. I.V. apomorphine HCl as well as 0.16 mg./kg. I.V. desacetyl lanatoside-C,* indicating that the CT-zone had been incompletely ablat

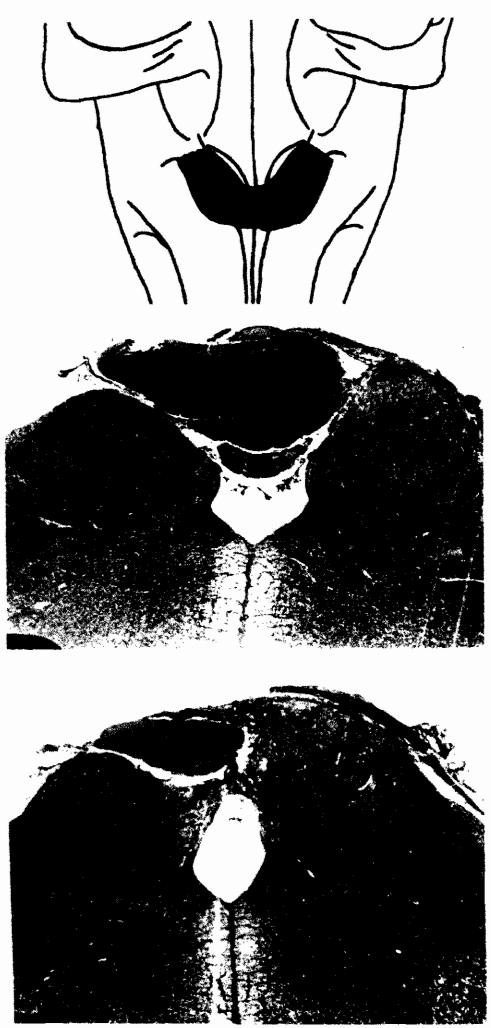
* Desacetyl lanatoside-C, according to the manufacturer, has the same toxicity as lanatoside-C. Therefore, the desacetyl analogue was administered in doses found to be effective for lanatoside-C.

The second dog was refractory to 3.0 and 6.0 mg./kg. I.M. nicotine bitartrate and 3.0 mg./kg. I.M. lobeline sulfate, as well as to 100 µg./kg. I.V. apomorphine HCl and 0.16 mg./kg. I.V. desacetyl lanatoside-C. The dog vomited, however, following 200 µg./kg. I.V. apomorphine HCl, indicating perhaps that a few receptor cells in the CT-zone still remained functional.

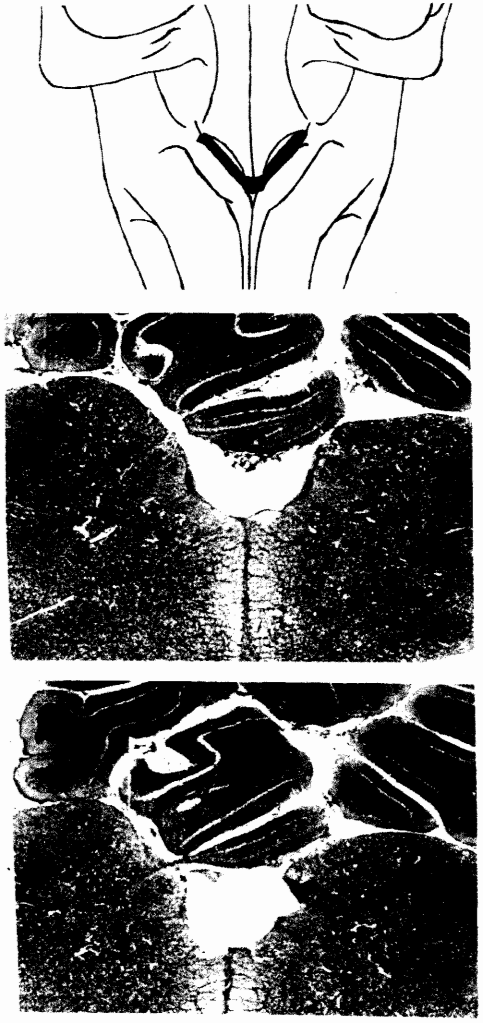
Of the nine dogs described above, only four gave evidence of having had the CT-zone effectively removed by the criterion of refractoriness to at least 100 µg./kg. of apomorphine HCl. However, all nine of the dogs showed refractoriness of some degree to the emetic actions of nicotine and/or lobeline.

Results of CT-zone ablation in cats are presented in table 4 where it can be seen that five chronic cats, which became refractory to the emetic action of apomorphine and/or desacetyl lanatoside-C as a result of trigger zone ablation, exhibited only inconsistent emetic refractoriness to the same dose of nicotine and lobeline as used in the dogs. Indeed, cats 32 (see figure 2) and 36, which were insensitive to the emetic actions of standard test doses of both apomorphine and desacetyl lanatoside-C, vomited frequently following injections of nicotine and lobeline.

In view of the relative inability of CT-zone ablation to prevent nicotine-and lobeline-induced emesis in cats, it was considered possible that afferent emetic pathways adjacent to the CT-zone might be involved in the vomiting. Therefore, a cat was prepared in which the superficial medullary structures, from the lateral border of the fourth ventricle to the lateral margin of the clava, and extending from the obex to the restiform body, were destroyed by thermal cauterization. This cat (cat 42 - figure 2) was refractory to the emetic actions of apomorphine HCl (25 mg./kg. S.C.), nicotine bitartrate (3.0 and 6.0 mg./kg. I.M.) and lobeline sulfate (2.0 and 6.0 mg./kg. I.M.). The functional integrity of the medullary reticular vomiting center was affirmed by the emetic effectiveness of oral copper sulfate and intravenous Veriloid. This cat also vomited to intravenous pilocarpine,



CAT 42



CAT 32

CAT 40

Table 4

EFFECT OF EMETIC DRUGS ON CATS WITH CHRONIC CT-ZONE LESIONS

	Apomorphine HCl 25 mg./kg. S.C.	Desacetyl Lanatoside-C 0.16 mg./kg. I.V.	Nicotine Bitartrate 3.0 mg./kg. I.M.	Lobeline Sulfate 2.0 mg./kg. I.M.
Cat # 32	- -	-	- / - /	/ -
Cat # 35	/	- -	/ - / /	/ /
Cat # 36 (*)	- -	-	/ - / - /	- -
Cat # 43	/	-	/ / /	/ -
Cat # 44 (")	/ /	-	/ - - / /	/

/ = Cat vomited.

- = No vomiting response evoked.

(*) = Cat responded positively three times to 6.0 mg./kg. nicotine bitartrate.

(") = Cat vomited to 3.0 mg./kg. nicotine bitartrate after right subclavian and left mid-cervical vagotomy.

but only after an abnormally long latency of more than 6 hours.

A series of four cats was then prepared with superficial medullary lesions which were parallel and lateral to the emetic CT-zone, but did not include the CT-zone proper. The lesions also cut across the mid-line at the level of the obex, thus forming a continuous incision from the restiform body on one side, to the obex, across the mid-line, and then to the opposite restiform body. All four cats vomited in response to apomorphine, desacetyl lanatoside-C, nicotine bitartrate and lobeline sulfate. This suggested the possibility that medially terminating vagal afferents contributed to the emetic response. Thus, two of these four cats were vagotomized by the transthoracic approach immediately above the diaphragm. Both cats vomited in response to nicotine and one also vomited after a test with lobeline. A vocal cord was then removed in one of these supradiaphragmatically vagotomized cats and a chronic tracheal fistula established in the other (cat 40 - figure 2). Following these procedures, both animals were vagotomized in the mid-cervical region. Vomiting was again evoked with nicotine bitartrate in both these cats. Thus, with the vagi excluded as "non-essential" to the response, the possibility remained that certain central afferent pathways, which could contribute to the vomiting, may have been spared by the superficial medullary lesions already described. Hence, a series of extramedullary lesions was performed so as to interrupt definitely all accessible ascending and descending afferents (see table 5).

2. Acute Extramedullary Lesions. Positive responses to nicotine were obtained in the following acute experiments: a) decerebration and bilateral mid-cervical vagotomy, b) decerebration and spinal cord transection at the level of the first thoracic vertebra, c) decerebration and bilateral section of cranial nerves V, IX, X, XI, and XII. The last one of these preparations retched several times following the nicotine bitartrate but it did not vomit owing to severe impairment of oropharyngeal function. Another cat was prepared in which the first three lesions were combined, namely, decerebration, bilateral mid-cervical vagotomy, and spinal

Table 5

EFFECT OF ACUTE AND CHRONIC EXTRAMEDULLARY LESIONS
ON EMETIC RESPONSE TO NICOTINE BITARTRATE (3.0 mg./kg. I.M.)

PROCEDURE	No. tested	No. vomited	Average latency (min.)
ACUTE			
Decerebration			
& Mid-Cervical Vagotomy	1	1	2.5
& Spinal Transection (T-2)	3	2	6.5
& Section of Nerves V, IX, X, XI & XII	1 (*)	1 (**)	4
& Spinal Transection (T-1) plus Mid-Cervical Vagotomy	1	0	-
Mid-Cervical Vagotomy			
& Spinal Transection (T-5)	4	2	13
& Spinal Transection (T-1)	3	0	-
CHRONIC			
Spinal Transection (T-5)	1	1	15
Spinal Transection (T-2)	1	1	5
Supradiaphragmatic Vagotomy	1	1	3
& Spinal Transection (T-4) (#)	3	3	6
& Spinal Transection (C-8) (#)	2	2	10
Mid-Cervical Vagotomy			
& Dorsal Rhizotomy (T-1 to T-10) (#)	1	1	3
Dorsal Rhizotomy (C-8 to T-7)	1	0	-
& Spinal Transection (T-7) (#)	1 (*)	1	7
& Right Subclavian & Left Mid-Cervical Vagotomy (#)	1 (*)	1	17
& Mid-Cervical Vagotomy	1 (*)	1	7

(*) = Tested with 6.0 mg./kg. nicotine bitartrate.
(**) = Retched only, (See RESULTS.)
(#) = Also vomited to 2.0 mg./kg. lobeline sulfate.

cord transection at T-1. This animal failed to vomit to nicotine bitartrate but it did vomit to Veriloid. A bilateral mid-cervical vagotomy in combination with spinal cord transection at T-1 was then performed in three other cats under ether anesthesia and the animals were tested one hour after discontinuation of the anesthetic. All of these animals were refractory to the emetic effect of nicotine bitartrate at the dose level of 3.0 mg./kg. I.M. One of these animals vomited subsequently in response to intravenous pilocarpine.

In order to determine the extent of spinal cord involvement in nicotine-induced vomiting, a series of four cats was prepared acutely with spinal cord transection at T-5 combined with bilateral mid-cervical vagotomy so as to exclude all abdominal afferents. Two of the four animals vomited following nicotine bitartrate, thus indicating that any remaining spinal afferents involved in nicotine-induced emesis must traverse the upper thoracic dorsal roots. It was concluded from these acute experiments that the site of emetic action of nicotine was in the trunk and required vagal innervation as well as spinal afferents.

3. Chronic Extramedullary Lesions. Since in acute experiments there is the possibility that the emetic refractoriness is due to a non-specific neuronal depression from the surgical trauma, another series of cats was prepared with chronic extramedullary lesions of portions of the nervous system. An attempt was made thereby to determine the relative contribution of receptor sites in the abdominal and thoracic cavities. Three chronic cats were prepared with supradiaphragmatic vagotomy in combination with spinal cord transection at T-4. All three animals vomited following 3.0 mg./kg. I.M. nicotine bitartrate and each of two cats vomited in response to 2.0 mg./kg. I.M. lobeline sulfate. Chronic spinal cord transection at the level of the eighth cervical segment combined with supradiaphragmatic vagotomy in two animals also failed to make cats insensitive to the emetic action of 3.0 mg./k nicotine and 3.0 mg./kg. lobeline.

From the acute experiments described above, it would appear that emetic receptor sensitive to nicotine are located below the neck and that certain of the afferent

pathways concerned traverse the upper thoracic dorsal roots. On the other hand, results from the chronic experiments, when interpreted in the light of information gained from the acute experiments, demonstrated the importance of the thoracic component of the vagus nerves. In order to delimit further the spinal segments involved, the dorsal roots of a cat were sectioned bilaterally from T-1 through T-10 and the vagi cut mid-cervically. This cat vomited in response to both nicotine and lobeline. It therefore appeared that afferent emetic fibers enter the spinal cord below the tenth thoracic segment as well as via the upper thoracic dorsal roots, while others traverse the vagus nerves.

In order to establish more definitely whether this is the case, chronic animals were prepared in which a bilateral dorsal rhizotomy was performed from C-8 to the mid-thoracic region and the spinal cord transected at the level of the lowest dorsal root section. In this way, the upper thoracic efferent roots were left intact, allowing the use of most of the intercostal musculature. The first of these cats vomited three minutes after intramuscular injection of 3.0 mg./kg. of nicotine bitartrate. The second cat was refractory to the emetic action of 3.0 but not 6.0 mg./kg. nicotine bitartrate and 2.0 mg./kg. lobeline sulfate. The capability of the second cat to vomit having been demonstrated, the right vagus nerve was then sectioned intrathoracically just below the right subclavian artery and the left vagus nerve was sectioned mid-cervically. The cat was tested a few days later and it vomited following 6.0 mg./kg. nicotine bitartrate, with a prolonged latency (17 minutes). One more animal was prepared with right subclavian and left cervical vagotomy combined with bilateral dorsal rhizotomy of segments C-8 through T-5 and spinal transection at T-5. The cat vomited to lobeline sulfate (3.0 mg./kg. I.M.) and to Veriloid (0.05 mg./kg. I.V.) but it did not vomit following a second injection of the same dose of lobeline sulfate, or after nicotine bitartrate (6.0 mg./kg. I.M.).

In order to exclude the possibility that afferent impulses enter the vagus nerves between the subclavian and mid-cervical regions, bilateral dorsal rhizotomy of segments C-8 through T-8 and spinal transection at T-8 were combined with bilateral mid-cervical vagotomy in one chronic cat. Thus, the deafferentation of this animal was similar to that of the three acute preparations, previously described, which had resulted in unresponsiveness to 3.0 mg./kg. nicotine bitartrate. This chronic animal vomited following intramuscular injection of 6.0 mg./kg. of this drug with a latency of 5 minutes.

4. Further Analysis of Medullary Lesions. The aforementioned series of extramedullary lesions effectively deafferented the medulla oblongata without preventing vomiting to very large doses of nicotine and lobeline, but the emetic thresholds definitely were elevated. The only medullary lesion in the cat which had abolished the emetic response to all doses of these agents tested was the broad superficial ablation of the structures lateral from the floor of the fourth ventricle to the lateral margin of the clava, between the obex and the restiform bodies including the CT-zone. In order to determine the degree of participation of the CT-zone in the vomiting response to nicotine, two cats were subjected to the extensive medullary lesion just described but with an attempt to spare the area postrema. Both cats vomited to apomorphine HCl and to nicotine bitartrate (3.0 mg./kg. I.M.). One of these cats also vomited in response to desacetyl lanatoside-C. This cat was subjected to right subclavian and left mid-cervical vagotomy. The animal again vomited in response to 3.0 mg./kg. I.M. nicotine bitartrate, thus demonstrating the importance of the CT-zone as a receptor site for nicotine-induced emesis.

The necessity of interrupting the three afferent emetic pathways is confirmed by deafferenting the trunk in a cat with an effective chronic CT-zone ablation. An abbreviated protocol of the experiments performed on this cat (No. 36) is given below:

10/11/56 CT-zone ablation.

10/22/56 3.0 mg./kg. I.M. nicotine bitartrate. Vomited after 14 minutes.

10/24/56 2.0 mg./kg. I.M. lobeline sulfate. No vomiting.

10/26/56 25 mg./kg. S.C. apomorphine HCl. No vomiting.

10/29/56 3.0 mg./kg. I.M. nicotine bitartrate. No vomiting.

10/31/56 2.0 mg./kg. I.M. lobeline sulfate. No vomiting.

11/2/56 3.0 mg./kg. I.M. nicotine bitartrate. Vomited after 10 minutes.

11/6/56 3.0 mg./kg. I.M. nicotine bitartrate. No vomiting.

11/8/56 0.16 mg./kg. I.V. desacetyl lanatoside-C. No vomiting.

11/13/56 6.0 mg./kg. I.M. nicotine bitartrate. Retched after 18 minutes.

11/21/56 6.0 mg./kg. I.M. nicotine bitartrate. Vomited after 11 minutes.

11/28/56 6.0 mg./kg. I.M. nicotine bitartrate. Vomited after 19 minutes.

12/7/56 3.0 mg./kg. I.M. nicotine bitartrate. Vomited after 8 minutes.

1/22/57 25.0 mg./kg. S.C. apomorphine HCl. No vomiting.

1/25/57 Left vocal cord removed.

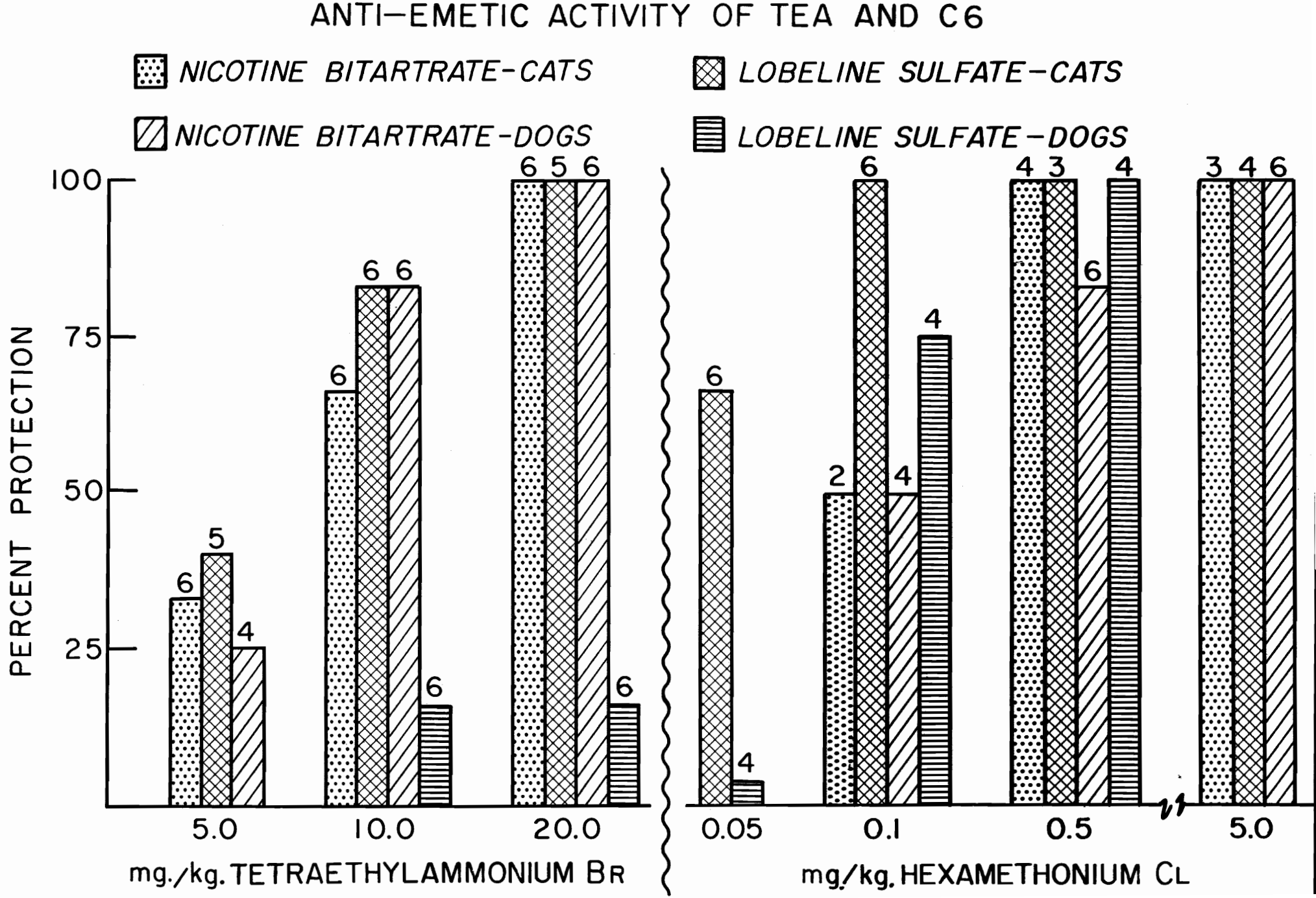
1/31/57 Bilateral mid-cervical vagotomy, bilateral dorsal rhizotomy (C-8 to T-8) and spinal transection (T-8).

2/3/57 6.0 mg./kg. I.M. nicotine bitartrate. No vomiting or signs of vomiting

2/5/57 6.0 mg./kg. I.M. nicotine bitartrate. No vomiting or signs of vomiting

C. Anti-Emetic Drug Studies.

The results of tests with TEA and C6, as antagonists of the emetic action of nicotine and lobeline in both cats and dogs, are shown in figure 3. It will be seen that the uniformly effective emetic doses of 1.5 mg./kg. I.M. nicotine bitartrate and 0.5 mg./kg. I.M. lobeline sulfate in cats were antagonized by prior administration of 20 mg./kg. I.M. of TEA. The same dose of TEA also was effective in dogs against nicotine bitartrate but not against lobeline sulfate. Indeed, TEA was not effective against lobeline-induced emesis in the dog in doses up to 40 mg./kg. In those animals in which emesis was blocked by TEA, the emetic prodromata were also blocked. Relaxation of the nictitating membrane was frequently, though not consistently, observed in protected cats but this was rarely seen in dogs, except


ANTI-EMETIC ACTIVITY OF TEA AND C6
NICOTINE BITARTRATE-CATS
NICOTINE BITARTRATE-DOGS
LOBELINE SULFATE-CATS
LOBELINE SULFATE-DOGS
PERCENT PROTECTION
100
75
50
25
6
5
4
6
6
6
6
5
6
6
6
6
4
6
2
6
4
4
4
3
6
4
3
4
6
5.0
10.0
20.0
mg./kg. TETRAETHYLAMMONIUM BR
0.05
0.1
0.5
5.0
mg./kg. HEXAMETHONIUM CL

failed to inhibit significantly the vomiting to 1.5 mg./kg. nicotine bitartrate in the dog, in spite of the fact that this dose of atropine caused depression and ataxia. The dose of 3.0 mg./kg. S.C. chlorpromazine caused moderate nervous system depression and 6.0 mg./kg. caused marked depression of the animals tested. The latency of vomiting to nicotine and lobeline was not prolonged in cats but there was an apparent increase in latency in dogs following administration of nicotine.

DISCUSSION

Possible sites of emetic action of nicotine and lobeline, taken into consideration in the present study, are as follows: a) CT-zone; b) forebrain; c) cranial afferents; d) abdominal loci; e) thoracic loci. The strongest support for the CT-zone as the emetic receptor site for these alkaloids is obtained from the dog experiments in which all tests in CT-zone ablated animals demonstrated some degree of refractoriness to nicotine, at least to the extent of protection against the minimum uniformly effective emetic dose established in normal dogs.

In the cat, on the other hand, emetic responses to suprathreshold doses of nicotine and lobeline were only inconsistently blocked by ablation of the CT-zone. In view of the facts that protection from the emetic effects of radiation in the cat also was obtained inconsistently after CT-zone ablation and that protection regularly followed abdominal denervation (Borison, 1957), it appeared possible that the same pattern of innervation might apply to nicotine-induced emesis.

The possible contribution of peripheral afferents to the vomiting evoked by nicotine was attacked in two ways. First, an attempt was made to interrupt spinal visceral afferents at the medullary level, by placing a bilateral incision in the dorsal surface of the medulla lateral to and parallel with the area postrema. The rationale for this procedure is provided by the histological data of Kuru (1955), Kuru and Sugihara (1956), and Liu (1956), which demonstrate terminations from thoracic, lumbar, and sacral afferents in the vicinity of the dorsal vagal nuclei. This experimental approach did not elevate the emetic threshold to nicotine, either by itself or in combination with mid-cervical vagotomy. The second approach for interruption of spinal visceral afferents was the direct surgical section of afferent pathways at the segmental level. This is most readily accomplished in the acute decerebrate preparation under ether anesthesia. The emetic response to a suprathreshold dose of nicotine in the cat was not prevented by the combination of decerebration with section of cranial nerves V, IX, X, XI, and XII, or by decerebration and high spinal cord section.

In contrast, when afferents were interrupted acutely by spinal transection in combination with vagotomy but without decerebration, twice the minimum uniformly effective dose of nicotine failed to evoke emesis. This provided support for the suggestion that peripheral afferents contribute to the emetic response. However, negative results from acute experiments must be substantiated in chronic preparations. Whereas data obtained in preparations with chronic visceral deafferentation did support the results obtained from the acute experiments, namely, by protecting against the same emetic dose level, vomiting could be evoked by still higher doses of nicotine.

Since the separate procedures of trunk deafferentation and CT-zone ablation served independently to elevate the emetic threshold, it follows that the combination of these procedures might eliminate the residual sensitivity to nicotine. The combination of these operations blocked the vomiting to the highest dose level of nicotine tested in this study, that is, 6 mg./kg. administered intramuscularly.

Hence, it is evident that stimulation of more than a single receptor site is responsible for the emetic response to nicotine. Further support for a dual mechanism of emetic stimulation was obtained by the surgical procedure of extending the CT-lesion laterally so as to include, in addition, the visceral afferents coursing over the dorsal surface of the medulla. This procedure also resulted in refractoriness to the highest dose of nicotine employed.

The participation of vagal afferents in the emetic response was demonstrated by the fact that mid-cervical vagotomy in combination with high cord section regularly caused an elevation in threshold, whereas cord section alone did not. The effect of mid-cervical vagotomy also was manifest at times by an increase in the latency of vomiting. In contrast, supradiaphragmatic vagotomy was ineffective in producing detectable changes in threshold or latency. This result, coupled with the fact that spinal deafferentation inclusive of the upper thoracic segments

was required in order to elevate the emetic threshold, indicates that trunk receptors for nicotine are located in the thorax as well as in the abdomen.

The importance of the vagus as an afferent source of emetic impulses has long been appreciated. Indeed, the emetic action of veratrum at the nodose ganglion of the vagus (Borison and Fairbanks, 1952) probably represents in large measure drug facilitation of subliminal afferent vagal activity. Accordingly, consideration must be given to the effect of lesions in the dorsal vagal nuclei of the medulla. It is evident that the threshold elevating effect of CT-zone ablation on nicotine-induced emesis cannot be attributed to damage of the dorsal vagal nuclei since vagotomy alone produced no such effect. On the other hand, failure to block nicotine-induced vomiting by the medullary lateral lesions, which were designed to interrupt spinal visceral afferents centrally but which avoided the CT-zone, may have been the result of central vagal sparing since cord section alone was ineffective in blocking the vomiting. Thus one could predict that the most effective central lesion would include the vagal nuclei medially, the CT-zone in the area postrema, and the spinal visceral afferent pathways laterally, all of which contribute to the emetic response.

Many species differences exist in responses to emetic stimuli. For example, the effective emetic dose of apomorphine in the cat is approximately 1000-fold greater than in the dog, and ergot, which readily produces vomiting in dogs, fails completely to evoke emesis in the cat. Chlorpromazine, on the other hand, which serves to protect dogs against certain centrally-acting emetic agents, has exhibited no protective effect in cats. From the morphological standpoint, it has been difficult in the dog to separate surgically the receptor elements for apomorphine and the cardiac glycosides; in contrast, this separation of receptors has been easily attained in the cat. The RESULTS show that refractoriness to I.V. cardiac glycosides results more consistently from CT-zone ablation than does refractoriness to apomorphine. This finding confirms results previously reported

from this laboratory (Borison, 1957). Differentiation of receptors for nicotine from those for apomorphine and the cardiac glycosides is provided by anti-emetic protection as well as by surgical fractionation of the CT-zone. TEA blocks the vomiting response to nicotine, in dogs as well as cats, but does not alter the response to the cardiac glycosides and apomorphine (Busse and Lendle, 1953). Chlorpromazine, in contrast, protects dogs against apomorphine but not against nicotine (see RESULTS) and the cardiac glycosides (Brand et al., 1954; Glaviano and Wang, 1955).

The apparent discrepancy in the effectiveness of CT-zone ablation against nicotine-induced vomiting in dogs versus cats finds its counterpart in X-radiation-induced emesis. The most plausible explanation for the species difference is that central pathways for afferent emetic impulses are more tightly funneled through the region of the CT-zone in the dog than in the cat. Thus a discrete lesion in the CT-zone of the dog would be expected to interrupt more emetic afferents of different origin than it would in the cat. This could explain also why the receptor elements for the cardiac glycosides and apomorphine are not easily separated by surgical means in the dog.

At first sight it would appear that nicotine might be acting at ganglionic sites to produce emesis. The fact that TEA and C6 block nicotine-induced vomiting seems to support this postulate. However, nicotine and lobeline are known to stimulate many extra-ganglionic loci, for example, sensory receptors in the skin and mesentery (Brown and Gray, 1948), carotid and aortic chemoreceptors (Moe et al., 1948), and pleural pain receptors (Eckenhoff and Comroe, 1951). Eckenhoff and Comroe have shown further that premedication with TEA prevents lobeline-induced substernal pain. In addition, the direct vasoconstrictive action of nicotine on the vascular smooth muscle of the perfused rabbit ear can be eliminated by injection of TEA or C6. Thus, it can be seen that the classical concept of a functional action of

nicotine and lobeline, and of the "ganglionic-blocking agents" TEA and C6, does not explain adequately the recent findings with these substances. Similarly, it is evident that the loci for emetic action of nicotine and lobeline elucidated in the present study also are extra-ganglionic.

SUMMARY

The emetic action of nicotine and lobeline was studied in cats and dogs. The minimal uniformly effective emetic doses were found to be 1.5 mg./kg. I.M. nicotine bitartrate and 0.5 mg./kg. I.M. lobeline sulfate. In terms of the alkaloid base, the dose-response relationship coincided, for practical purposes, at all dose levels studied.

Sixty-six cats and ten dogs were used to establish the locus of the emetic action of the alkaloids. It was found, in cats, that the agents stimulated two different sites of action, namely, a peripheral locus (or loci) as well as the CT-zone. Therefore, in order to eliminate the vomiting response to nicotine and lobeline in cats, it was necessary to combine the following procedures: spinal visceral deafferentation, vagotomy, and CT-zone ablation. The combination of these lesions was accomplished either by peripheral nerve sections in combination with CT-zone ablation or by a broad medullary lesion which destroyed both the CT-zone and incoming visceral afferents. In dogs, CT-zone ablation alone sufficed to protect animals against the emetic effect of nicotine and lobeline. The implication of these results is discussed in light of investigations on species variations previously reported in this field.

Anti-emetic drug studies were also included in the present investigation. Tetraethylammonium (TEA) was effective in preventing emesis in response to nicotine in both cats and dogs, but it was effective only against lobeline in cats. Hexamethonium (C6) protected both species against uniformly effective emetic doses of nicotine and lobeline. Neither atropine nor chlorpromazine was found significantly to protect animals of either species against the emetic action of nicotine and lobeline.

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